



DEPARTMENT OF HEALTH & HUMAN SERVICES

PUBLIC HEALTH SERVICE  
NATIONAL INSTITUTES OF HEALTH

FOR US POSTAL SERVICE DELIVERY:

Office of Laboratory Animal Welfare  
6700B Rockledge Drive, Suite 2500, MSC 6910  
Bethesda, Maryland 20892-6910  
Home Page: <http://grants.nih.gov/grants/olaw/olaw.htm>

FOR EXPRESS MAIL:

Office of Laboratory Animal Welfare  
6700B Rockledge Drive, Suite 2500  
Bethesda, Maryland 20817  
Telephone: (301) 496-7163  
Facsimile: (301) 480-3387

September 16, 2022

Re: Animal Welfare Assurance  
A4051-01 [OLAW Case 1E]

Dr. Wayne Cascio  
Director of CPHEA  
U.S. Environmental Protection Agency  
109 TW Alexander Drive  
Durham, NC 27711

Dear Dr. Cascio,

The Office of Laboratory Animal Welfare (OLAW) acknowledges receipt of your September 9, 2022, letter reporting several instances of noncompliance with the PHS Policy on Humane Care and Use of Laboratory at the Environmental Protection Agency, Research Triangle Park, following up on an initial email notification on August 18, 2022. According to the information provided, OLAW understands during a post-approval monitoring (PAM) audit of a newly approved protocol, it was identified that rats were exposed to temperatures higher (100-101.5°F) than what was approved in the protocol (95-100°F). The animals were not monitored visually for signs of distress and instead were only observed sporadically, as evidenced by porphyrin staining around the eyes, hypersalivation, diarrhea, and behavior indicative of anxiety or stress. Thermal support was also not immediately provided to the anesthetized rats that were left unsupervised by students, who were unaware of the animals' surgical plane, during the conduct of post-exposure procedures. In addition, rats undergoing procedures under anesthesia or necropsy were not kept at a sufficient distance from conscious rats awaiting procedures, which may be stressful to the conscious animals.

The corrective actions consisted of the Principal Investigator (PI) working with inhalation engineering personnel to improve temperature control and ensure maintenance at the specified temperature range approved in the protocol. The PI and research team will undergo training to recognize adverse responses, actions to be taken if such responses are observed, and how to appropriately document the observed responses. The PI has ensured that there will be proper monitoring and support of anesthetized animals, as well as recording of the anesthetic regimen and responses. Appropriate separation of conscious animals from animals undergoing sedation or necropsy will also be ensured by the PI. The PI will submit an amendment recategorizing the animals exposed to higher temperatures to pain Category E, since these animals will undergo unalleviated painful or stressful procedures.

Based on the information provided, OLAW is satisfied that appropriate actions have been taken to investigate, correct and prevent recurrence of the noncompliance. Your prompt and thorough resolution of this matter is commendable and consistent with the PHS Policy philosophy of monitored self-regulation. We appreciate having been informed of this matter and find no cause for further action by this Office.

Page 2 – Dr. Cascio  
September 16, 2022  
OLAW Case A4051-1E

Sincerely,

**Neera V.**

**Gopee -S**

Neera V. Gopee, DVM, PhD, DACLAM, DABT  
Associate Director, Animal Welfare Policy  
Office of Laboratory Animal Welfare  
National Institutes of Health

Digitally signed by Neera V.  
Gopee -S  
Date: 2022.09.16 13:20:09  
-04'00'

cc: IACUC Chair

**McCoy, Devora (NIH/OD) [E]**

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**From:** McCoy, Devora (NIH/OD) [E]  
**Sent:** Friday, September 16, 2022 3:16 PM  
**To:** Cascio.wayne@epa.gov  
**Cc:** OLAW Division of Compliance Oversight (NIH/OD); Gavett, Stephen; graff.jaimie@epa.gov  
**Subject:** OLAW Case A4051-1E  
**Attachments:** Cascio USEPA 4051-1E.pdf

Good afternoon Dr. Cascio,

Attached please find Dr. Gopee's response to OLAW Case A4051-1E. If you have any questions, feel free to contact us by phone or by e-mail.

Best,  
Devora

Devora McCoy, BS, MBA  
Program Analyst  
Division of Compliance Oversight  
Office of Laboratory Animal Welfare  
National Institutes of Health  
301-435-2390

A4051-1E



**UNITED STATES ENVIRONMENTAL PROTECTION AGENCY**

Center for Public Health and Environmental Assessment  
109 T.W. Alexander Drive, Research Triangle Park, NC 27711

September 9, 2022

OFFICE OF  
RESEARCH AND  
DEVELOPMENT

Axel Wolff, M.S., D.V.M.  
Deputy Director  
Office of Laboratory Animal Welfare  
National Institutes of Health

Dear Dr. Wolff:

We are writing to report the final resolution of an adverse animal welfare incident at the US EPA Research Triangle Park (RTP) research program, USDA Certificate number 55-F-0001, Customer ID number 962; PHS Assurance # D16-00569, A4051-01; AAALAC Unit #000509, including measures taken by the program to ensure that these events will not be repeated. A preliminary report of this event was originally emailed to OLAW on Thursday, August 18.

Preliminary Findings Communicated Previously to OLAW:

The adverse event was first observed July 19-21 during post-approval monitoring (PAM) of a newly approved animal protocol. A draft summary of the observations was circulated to members of the EPA IACUC on July 31 and discussed in detail in an EPA IACUC meeting on August 17, 2022. This was the earliest the IACUC could meet to discuss this issue as several key members were out for a medical emergency, on leave, or official travel during the intervening days. The study had achieved its *in vivo* testing endpoints by July 21 and no further *in vivo* research is currently scheduled.

The goal of the approved research protocol is to determine the cardiovascular, pulmonary and behavioral impacts of very short-term exposures (30 to 40 minutes) to high temperatures (95 to 100 °F) in rats, in order to clarify the impact of heat on the body, address an important component of climate change, and provide information about the potential risk of such exposures which are increasing in incidence.

Key findings of the PAM were as follows:

- The temperatures in chambers used to expose rats to thermal stress were 100 to 101.5 °F, while the approved protocol stated the temperature would be 95 to 100 °F.
- Animals were only sporadically observed during the exposure period by the research team, though the approved protocol stated animals will be monitored visually for signs of distress during the exposure. Rats exposed to high temperatures were found during the PAM to have some or all of the following: porphyrin secretions around the eyes and

face, hypersalivation, diarrhea, and behaviors indicating anxiety or stress. These signs were not recognized as adverse by the research team.

- During procedures following the exposures, rats were unsupervised while under general anesthesia, and thermal support was not immediately provided to anesthetized animals. Students involved in the study did not know the status of rats under anesthesia.
- Rats which were undergoing procedures under anesthesia or necropsy were not kept at a sufficient distance from rats which were awake and conscious in their cages and awaiting their procedures, which could be stressful to the conscious rats.

Allowing temperatures to rise above the 95-100 °F approved range, failing to quickly provide thermal support and monitoring for anesthetized animals, failing to keep surviving animals sufficiently separate from dying animals, and failing to note through lack of observation that the animals in the high heat chambers were in serious distress are all significant welfare issues.

New Corrective Action Plan to Address the Animal Welfare Issues:

In consultation with the Attending Veterinarian and other members of the EPA IACUC, the principal investigator wrote a plan of corrective actions to address the animal welfare issues identified in the PAM. The EPA IACUC met on September 7, 2022 to discuss the plan, and approved it after making some minor modifications. The plan includes the following:

- The PI will work with inhalation engineering personnel to improve temperature control and ensure it is maintained in the appropriate range specified in the approved animal protocol.
- The PI and the research team will undergo training for recognition of adverse responses, what actions will be taken if such responses are observed, and how they will be documented. Some adverse responses require immediate cessation of the exposure, while others are indicative of some stress, but only require continued vigilant monitoring during the exposure.
- The PI has ensured that there will be proper monitoring and support of anesthetized animals and recording of the anesthetic regimen and responses.
- The PI has ensured that there will be proper separation of conscious awake animals separate from animals undergoing sedation or necropsy.
- The PI is submitting an amendment to recategorize animals exposed to the higher temperatures to Category E, indicating potentially painful or stressful procedures unrelieved by anesthetics, analgesics, or tranquilizer drugs.

After the engineering controls have been implemented, the PI and the research team have taken the training for recognition of adverse responses, and the PI has taken the other steps outlined above, then the IACUC will allow the work in this approved protocol to continue. We are satisfied that the PI has recognized the significance of the animal welfare issues and made the appropriate changes to correct the problems.

We hope these measures satisfactorily address the issues raised by this incident. Please contact Stephen Gavett (919-541-2555, [Gavett.stephen@epa.gov](mailto:Gavett.stephen@epa.gov)) or Jaimie Graff (919-541-0690, [Graff.jaimie@epa.gov](mailto:Graff.jaimie@epa.gov)), Animal Resources Program Office, if you have further questions.

Sincerely,

**WAYNE  
CASCIO**

Digitally signed by  
WAYNE CASCIO  
Date: 2022.09.09  
09:54:19 -04'00'

Wayne E. Cascio, MD, FACC  
Director, Center for Public Health and Environmental Assessment  
Institutional Official  
Office of Research and Development  
U.S. Environmental Protection Agency

**McCoy, Devora (NIH/OD) [E]**

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**From:** Graff, Jaimie <Graff.Jaimie@epa.gov>  
**Sent:** Friday, September 9, 2022 10:45 AM  
**To:** OLAW Division of Compliance Oversight (NIH/OD)  
**Cc:** Gavett, Stephen; (b) (6)  
**Subject:** [EXTERNAL] FW: Preliminary notice of animal welfare issue  
**Attachments:** Final Report to OLAW 9.8.2022 \_WEC.pdf

**Follow Up Flag:** Follow up  
**Flag Status:** Flagged

Good morning;

Attached please find the final report for US EPA, Office of Research and Development, Research Triangle Park, NC; OLAW Assurance number D16-00569, A4051-01 concerning an adverse event impacting animal welfare and noncompliance which was first observed July 19-21 during post-approval monitoring (PAM) of a newly-approved animal protocol. Please let us know if OLAW is satisfied with how our program handled this incident or if further action is required.

Thank you;

Jaimie

Jaimie Graff, MA, CPIA | Director, Animal Resources Program Office | US EPA/ORM/RSCD/FRCB | Phone: 919-541-0690 | Cell: 984-484-0332

**From:** Gavett, Stephen <Gavett.Stephen@epa.gov>  
**Sent:** Friday, September 9, 2022 10:35 AM  
**To:** Graff, Jaimie <Graff.Jaimie@epa.gov>  
**Subject:** FW: Preliminary notice of animal welfare issue

**From:** OLAW Division of Compliance Oversight (NIH/OD) <olawdco@od.nih.gov>  
**Sent:** Thursday, August 18, 2022 2:07 PM  
**To:** Gavett, Stephen <Gavett.Stephen@epa.gov>  
**Cc:** OLAW Division of Compliance Oversight (NIH/OD) <olawdco@od.nih.gov>  
**Subject:** RE: Preliminary notice of animal welfare issue

Good afternoon Dr. Gavett,

Thank you for sending us this preliminary report. We look forward to receiving the final report once the investigation is complete.

Best,  
Devora

Devora McCoy, BS, MBA  
Program Analyst  
Division of Compliance Oversight  
Office of Laboratory Animal Welfare

**From:** Gavett, Stephen <Gavett.Stephen@epa.gov>  
**Sent:** Thursday, August 18, 2022 1:43 PM  
**To:** OLAW Division of Compliance Oversight (NIH/OD) <olawdco@od.nih.gov>  
**Cc:** Cascio, Wayne <Cascio.Wayne@epa.gov>; Graff, Jaimie <Graff.Jaimie@epa.gov>; Jarrell, Leslie <Jarrell.Leslie@epa.gov>; (b) (6)  
**Subject:** [EXTERNAL] Preliminary notice of animal welfare issue

To the Division of Compliance Oversight:

As chair of our IACUC, I am writing to provide preliminary notice of an adverse event impacting animal welfare which was identified at our institution (US EPA, Office of Research and Development, Research Triangle Park, NC; OLAW Assurance number D16-00569, A4051-01). The adverse event was first observed July 19-21 during post-approval monitoring (PAM) of a newly-approved animal protocol. A draft summary of the observations was circulated to members of the EPA IACUC on July 31, and discussed in detail in an EPA IACUC meeting on August 17, 2022. This was the earliest the IACUC could meet to discuss this issue as several key members were out for a medical emergency, on leave, or official travel during the intervening days.

The goal of the approved research protocol is to determine the cardiovascular, pulmonary and behavioral impacts of very short-term exposures (30 to 40 minutes) to high temperatures (95 to 100 °F) in rats, in order to clarify the impact of heat on the body, address an important component of climate change, and provide information about the potential risk of such exposures which are increasing in incidence.

Key findings were as follows:

- The temperatures in chambers used to expose rats to thermal stress were 100 to 101.5 °F, while the approved protocol stated the temperature would be 95 to 100 °F.
- Animals were only sporadically observed during the exposure period by the research team, though the approved protocol stated animals will be monitored visually for signs of distress during the exposure. Rats exposed to high temperatures were found during the PAM to have some or all of the following: porphyrin secretions around the eyes and face, hypersalivation, diarrhea, and behaviors indicating anxiety or stress. These signs were not recognized as adverse by the research team.
- During procedures following the exposures, rats were unsupervised while under general anesthesia, and thermal support was not immediately provided to anesthetized animals. Students involved in the study did not know the status of rats under anesthesia.
- Rats which were undergoing procedures under anesthesia or necropsy were not kept at a sufficient distance from rats which were awake and conscious in their cages and awaiting their procedures, which could be stressful to the conscious rats.

Allowing temperatures to rise above the 95-100 °F approved range, failing to quickly provide thermal support and monitoring for anesthetized animals, failing to keep surviving animals sufficiently separate from dying animals, and failing to note through lack of observation that the animals in the high heat chambers were in serious distress are all significant welfare issues.

The principal investigator will be providing a plan of corrective actions to address these animal welfare issues. No further experiments will be allowed using this protocol until these corrective actions are approved by the IACUC and implemented by the investigator. A final report giving all details of the animal welfare issues identified here will be provided to OLAW within the next few days.

Please let me know if you need further information.

Sincerely,

Stephen Gavett, Ph.D., D.A.B.T.

Research Biologist, Chair EPA Health IACUC  
Cardiopulmonary and Immunotoxicology Branch  
CIB PHITD CPHEA ORD USEPA  
Tel. 919-541-2555

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**To:** OLAW Division of Compliance Oversight (NIH/OD)  
**Cc:** Cascio, Wayne; Graff, Jaimie; Jarrell, Leslie; Hoopes, Maria  
**Subject:** [EXTERNAL] Preliminary notice of animal welfare issue

**Follow Up Flag:** Follow up  
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Research Biologist, Chair EPA Health IACUC  
Cardiopulmonary and Immunotoxicology Branch  
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Tel. 919-541-2555

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**McCoy, Devora (NIH/OD) [E]**

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**Subject:** RE: Preliminary notice of animal welfare issue

Good afternoon Dr. Gavett,

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Best,  
Devora

Devora McCoy, BS, MBA  
Program Analyst  
Division of Compliance Oversight  
Office of Laboratory Animal Welfare  
National Institutes of Health  
301-435-2390

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Please let me know if you need further information.

Sincerely,

Stephen Gavett, Ph.D., D.A.B.T.

Research Biologist, Chair EPA Health IACUC  
Cardiopulmonary and Immunotoxicology Branch  
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